REPRINTED FROM

UNIVERSITY
MEDICAL MAGAZINE

EDITED UNDER THE AUSPICES OF THE ALUMNI AND FACULTY OF MEDICINE OF THE UNIVERSITY OF PENNSYLVANIA

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Vol. IX. MAY, 1897. No. 8.

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PUBLISHED MONTHLY BY
UNIVERSITY OF PENNSYLVANIA PRESS,
133 FILBERT ST., PHILADELPHIA, PA.

PRICE, $2.00 A YEAR IN ADVANCE.

Entered at the Post-office at Philadelphia, and admitted for transmission through the mails at second-class rates.

SEPTEMBER, 1897

HEREDITARY LATERAL SCLEROSIS.

BY AUGUSTUS A. ESHNER, M.D.,

Professor of Clinical Medicine in the Philadelphia Polyclinic; Visiting Physician to the Philadelphia Hospital.

HEREDITARY LATERAL SCLEROSIS.[1]

By Augustus A. Eshner, M.D.,

Professor of Clinical Medicine in the Philadelphia Polyclinic; Visiting Physician to the Philadelphia Hospital.

M. G., a widow, 59 years old, applied at the Philadelphia Orthopedic Hospital and Infirmary for Nervous Diseases, in the clinical service of Dr. S. Weir Mitchell, on January 15, 1897, complaining of twitching of the legs, both subjective and objective, that had been noticed for a period of ten years. Similar muscular manifestations had gradually extended to all parts of the body, including the head. The twitching was said to be worse during rest, and especially at night, and it was believed to persist during sleep, which was disturbed thereby, so that the patient was compelled to arise and walk about. On account of this annoyance she had not gone to bed at all for six weeks, simply reclining upon a sofa at night. There had never been a convulsion or loss of consciousness or any paralysis. The appetite was good, the tongue coated, the bowels constipated. From time to time hemorrhage took place from the bowels, probably in consequence of a hemorrhoidal condition. There was neither nausea nor vomiting, and no loss of flesh, no chill, fever, or sweating. There was headache every morning, lasting from twelve to twenty-four hours, and susceptible of relief by bromides. There was subjective vertigo. The prominent symptoms in the case were uninfluenced by heat, cold, dryness, or moisture. Gait and station were steady and exhibited no abnormality. The knee-jerks were exaggerated. When the patellar tendon was struck, in addition to the active extension of the leg, the thigh became flexed and the patient jumped visibly. Ankle-clonus was present on the right, but could not be elicited on the left. Coordination was good in the upper extremities and the reflexes were normal. There was no tremor of the extended hands and fingers. Sensibility was preserved. The pupils were equal and regular and reacted sluggishly to light. There was no nystagmus.

Examination of the ocular apparatus, by Dr. A. G. Thomson, yielded the following findings: V.= R. $\frac{20}{100}$; L. $\frac{3}{200}$. The pupils reacted normally both to light and in accommodation. *O. D.* The media were clear, the disk a trifle gray. The fundus was normal. *O. S.* Disk and fundus were normal. There was high myopia, and a macula was present on the cornea, resulting from measles in child-

[1] Read before the Section of Neurology of the American Medical Association, June 1897.

hood and impairing vision. The fields of vision for both form and color were normal. The muscular balance was well maintained.

The patient exhibited and was conscious of a general restlessness, to secure relief from which she sometimes tapped her foot, sometimes rocked from side to side, sometimes rotated her head. The action of the heart was rhythmic, its sounds clear. There was no difficulty in speech and none in swallowing. The complexion was muddy and the patient stated that she had been pale as long as she could remember. There was no spinal tenderness and no evidence of spinal deformity. There was no difficulty in micturition and the action of the sphincters was unimpaired. The blood was found to contain a full complement of red corpuscles, although the hemoglobin-valuation was only 50 per cent. There was no consanguinity between the patient and her husband. Her mother had suffered a good deal from headache, and a brother's son had been melancholy. There had been no difficulty in birth and no traumatism; and there was no history indicative of spinal meningitis or of syphilis.

A hesitant diagnosis of incipient lateral sclerosis was made in this case and the possible dependence of the lesion upon the state of the blood taken into consideration. When, however, the patient, a few weeks later, brought her son, and he too was found to be suffering from similar symptoms, the conclusion could hardly be avoided that we had here to deal with a mild degree of lateral sclerosis in parent and in child, and I am inclined to believe the disease to be hereditary, or at least familial. It is noteworthy that both patients exhibit manifest pallor, and this fact suggests the possibility of a common etiology, either the blood-state acting as a cause of the spinal degeneration or with this representing the common effect of some undetermined cause. Against this hypothesis is the fact that the spinal lesions of the profound anemias are situated by preference in the posterior columns, while in both of the cases here reported there is no evidence of posterior-column disease.

M. G. (a son of the patient whose case has just been reported), 18 years old, employed as a machinist, was born at term, without complication or instrumental aid. He had a convulsion at the age of three months, while nursing at the breast, during the period of dentition. He learned to walk and to speak readily and early. At the age of eleven months he suffered from the presence of spool-worms in the intestine, associated with attacks of crying and throwing back of the head. He had measles at the age of two years, and fever and ague at the age of eleven. On September 24, 1896, the patient was operated on for appendicitis successfully. He had for two months previously suffered from pain in the left lumbar region, and this had

persisted. His habits were good. He was a total abstainer from alcohol and from tobacco; he used no tea and but very little coffee. Four years before coming under observation he had been struck with a fist in the temporal region, losing consciousness temporarily, although only ringing in the ears followed for a few days. There was no history of masturbation or of venereal disease. The patient had complained of a sense of lightness in the head from childhood. On sudden change of position a mist would come before the eyes and quickly pass away. For a period of six months he had noticed that frequently there would occur an involuntary twitching of the left leg. He had never fallen or lost consciousness. He complained of a feeling of nervousness and often had a sense of trembling; at times he actually shivered. The appetite was good; at times pain followed the act of eating, together with acid eructations. The bowels were naturally constipated, but they were kept free by cod-liver oil, which the patient was taking as a nutrient. He had lost a considerable amount of flesh in the six months preceding the time he came under observation. About once a week he suffered from headache, lasting for two or three hours at a time, and being relieved by the use of bromides. He slept well, although he talked in his sleep and was at times restless. He had been pallid for five or six months. Gait and station were steady. The knee-jerks were deliberate, large, and exaggerated. Front-tap contraction could be elicited in the left leg; ankle-clonus also was present on the left; it was less distinct upon the right, unless the tendo Achillis was struck when the foot was flexed upon the leg. By this means ankle-clonus could be very readily induced on both sides. The induction of these reflexes was followed by fine tremor, especially marked in the thighs. When the partially flexed foot was tapped on the plantar aspect the foot was extended. The reflexes in the upper extremities and also the chin-jerk were active. The pupils were equal, regular, and reactive to light. There was no nystagmus. General sensibility was preserved. The cremasteric, abdominal, and epigastric reflexes were preserved. The action of the heart was rhythmic, its sounds clear. No physical abnormality could be detected in the situation of the abdominal uneasiness of which the patient complained. There was no spinal tenderness and none over the kidneys. It was further learned that for several years, until a bougie had been passed, there had been difficulty in the expulsion of urine, but there had never been any evidence of the presence of a urinary concretion. There was no difficulty in swallowing and no affection of speech. Dr. A. G. Thomson found no change in the fundus of either eye.

From a consideration of the symptomatology, and especially of

the physical phenomena, of the foregoing two cases the conviction can scarcely be escaped that the clinical manifestations depend upon sclerosis of the pyramidal fibres of the spinal cord. I prefer to speak of the probable pathologic process rather than employ the clinical designation spastic paraplegia or spinal spastic paralysis, inasmuch as the motor disability is as yet inconsiderable. Whether this process be primary or secondary I will not assume to state positively; but there is no tangible evidence of any antecedent condition upon which it could be held to be dependent, and in the absence of this I am disposed to view the pyramidal sclerosis as primary. A review of the literature upon the subject of spastic paraplegia does not entirely resolve the doubt as to the uncomplicated occurrence of primary lateral sclerosis, although the evidence, so far as it goes, tends to support such a possibility. In a fatal case of spastic paraplegia, reported by Strümpell (*Archiv für Psychiatrie*, Band x, 1880, p. 711), occurring in a man whose older brother presented like symptoms, together with others of multiple sclerosis, post-mortem examination disclosed symmetrically distributed primary sclerosis of the pyramidal tracts, most marked in the lumbar region, gradually diminishing in an upward direction, and not extending beyond the decussation in the medulla; together with sclerosis of the cerebellar tracts and the postero-internal columns of Goll (Strümpell, *Archiv für Psychiatrie*, Band xvii, 1886, p. 217). In other cases of combined system-disease of the spinal cord Strümpell (*Archiv für Psychiatrie*, Band xi, 1881, p. 27) found also primary degeneration of the pyramidal tracts. Minkowski (*Deutsches Archiv für klinische Medicin*, Band xxxiv, 1884, p. 433) has reported the case of a syphilitic woman, dead of pulmonary tuberculosis, in which, after death, sclerosis of the lateral pyramidal tracts and of the cerebellar tracts only was found. Déjerine and Sottas (*Archives de Physiologie normale et pathologique*, 1896, p. 630) have also reported a case of slowly developing spastic paraplegia, progressing for twelve years and then becoming stationary, in which, after death from pneumonia, there was found isolated and systematic sclerosis of the pyramidal fibres of the spinal cord and slight sclerosis of the columns of Goll, with integrity of the brain, the meninges, the spinal nerve-roots, and the spinal gray matter. Upon *a priori* grounds there is no obvious reason why primary sclerosis of the pyramidal tracts should not take place; and if, as seems probable, we may look upon locomotor ataxia as essentially dependent upon disease of the centripetal neuron we may equally look upon spastic paraplegia as dependent upon disease of the centrifugal neuron.

The more interesting feature of our cases, however, is their occurrence in parent and child. We have much to learn concerning the

hereditary and familial distribution of disease, and especially of diseases of the nervous system; but in the absence of definite knowledge upon the subject we may conceive of the existence of some developmental defect resulting either in gross structural abnormality, or in those undiscernible alterations in texture so delicate as to elude the most rigid physical scrutiny, yet capable of manifesting themselves in aberrant function, or finally in an undue vulnerability to morbific influences. A very considerable number of cases of spastic paraplegia of familial distribution have now been reported, but in many of these there have been present also symptoms of disease of other parts than the pyramidal fibres. Among the earliest are four cases reported by Seeligmüller (*Deutsche medicinische Wochenschrift*, 1876, Nos. 16, 17) and occurring in children the mothers of whose parents (cousins) were sisters. Three other children in the family were healthy. In two of the affected children there was, in addition to the spastic manifestations, also muscular atrophy, and in two there was impaired mobility of lips, palate, and tongue, with defect of speech. Somewhat later Dreschfeld (*Medical Times and Gazette*, February 9, 1878, p. 140) reported two cases of disseminated sclerosis in brothers 8 years and 9 months and 7 years and 4 months old respectively, presenting spastic phenomena. In one of these there had been convulsions in infancy.

In reporting a group of cases illustrative of the pathology of the spinal cord Strümpell (*Archiv für Psychiatrie*, Band x, 1880, p. 711) includes the two cases already referred to, occurring in brothers, which he considered clinically instances of spastic paralysis, although he appreciated that in the one, in which there was a history of convulsions in infancy, there were present also symptoms of multiple sclerosis.

Bloch (*Archiv für Psychiatrie*, Band xii, Heft 2, 1881, p. 470), in relating the history of a family presenting peculiarities in the knee-jerk, in connection with a neuropathic diathesis, refers to two brothers, 19 years and 17 years and 6 months old respectively, who exhibited manifestations of lateral sclerosis.

Pelizæus (*Archiv für Psychiatrie*, Band xvi, 1885, p. 698) has reported five cases in members of one family, although not of one generation, presenting symptoms of spastic paralysis, in conjunction with cerebral symptoms, which he attributes to multiple sclerosis.

Philip (*Brain*, viii, 1886, p. 520) has reported a family of nine children, in which the father presented symptoms of gradually advancing spastic paralysis, the youngest son early symptoms of the same order, and three other sons symptoms of pseudo-hypertrophic muscular paralysis.

Schultze (*Deutsche medicinische Wochenschrift*, April 11, 1889, p. 287) reports three cases, in two sisters and one brother, presenting

spastic manifestations in the lower extremities, in both girls associated with strabismus, and in one of them also with increased size of the head. The first child in the family, which was healthy, had been born without complication, while the subsequent labors were slow and difficult.

Gee (*St. Bartholomew's Hospital Reports*, 1889, Vol. xxv) has reported a father and a son and daughter who presented symptoms of spastic paraplegia, associated in father and son with wasting of muscles of the hands.

Latimer (*Transactions of the American Pediatric Society*, Vol. 1, 1890, p. 195) has reported two cases of spastic paraplegia in brother and sister, aged 20 and 18 years respectively, in the former of whom also speech was slow and thick, and there was occasionally involuntary discharge of urine and feces. There had, however, been no difficulty in birth, no convulsions, and no antecedent disease. The father was a chronic alcoholic.

Bernhardt (*Archiv für pathologische Anatomie und Physiologie und für innere Medicin*, Band cxxxvi, 1891, p. 59) has reported the case of a man, 46 years old, who presented symptoms of spastic paralysis, together with others indicative of involvement also of the pons and medulla, all being suggestive of multiple sclerosis, and three of whose brothers and also a sister presented similar symptoms.

Tooth (*St. Bartholomew's Hospital Reports*, Vol. xxvii, 1891, p. 7) reports four cases of what he believed to be sclerosis of the crossed pyramidal tracts, occurring in two brothers in different families, and presenting symptoms of spastic paraplegia, in two associated with stammering speech.

Krafft-Ebing (*Wiener klinische Wochenschrift*, 1892, No. 47, p. 681) reports three cases of spastic paraplegia in a sister and two brothers, which he thinks may be due to congenital hydromyelus.

Freud (*Neurologisches Centralblatt*, xii, Jahrg. 1893, p. 512) reports two brothers with spastic extremities, nystagmus, optic atrophy, convergent strabismus, and bradylalia, believed to be due to cerebral diplegia.

Strümpell (*Deutsche Zeitschrift für Nervenheilkunde*, Band iv, 1893, p. 172) cites the case of a man, presenting symptoms of spastic spinal paralysis, whose grandfather had for a long time suffered from "paralysis of the legs," and whose brother and father and two of the latter's brothers had a peculiar gait like the patient's. Of this disorder, which Strümpell designates the hereditary form of spastic paralysis, he considers the characteristics its occurrence only in males and its familial or hereditary distribution. The first symptoms appear at the age of 25 or 30, and consist in an alteration of the gait due to muscular

rigidity, without weakness, and which increases until the gait is spastic. The disorder progresses slowly, and only the lower extremities are involved.

Newmark (*American Journal of the Medical Sciences*, 1893, Vol. CV, p. 432) reports the case of sister and brother, 15 and 5 years old respectively, born without difficulty, who presented symptoms of spastic paraplegia, and whose mother and a sister exhibited increased reflexes. In a sister of the mother also the reflexes were exaggerated, and of her eight children the first was dead after delivery; the second was born after a difficult labor, had convulsions, and presented symptoms of bilateral spastic hemiplegia; the third labor was difficult; the fourth labor also was difficult, and the child exhibited increased reflexes; the fifth, sixth, and seventh labors were difficult, the last child dying after birth, and the other two presenting exaggerated reflexes. Newmark reports another family, of eleven children, of which four boys and a girl exhibited spastic symptoms, and two other girls and a boy increased reflexes. One of the boys and one of the girls presenting spastic manifestations had been delivered with forceps; and in the birth of one of the girls with increased reflexes, who died from "water on the brain," labor had lasted two days and nights, although delivery was non-instrumental. Newmark (*Medical News*, January 16, 1897) reports two additional cases of spastic paraplegia occurring in sisters, 6 and 4 years old respectively, in the birth of the older of whom forceps had been used. In both articulation was indistinct. Forceps had also been employed in the delivery of an older sister still, who, however, exhibited no spastic phenomena.

Souques (*Revue neurologique*, Tome III, 1895, p. 1) has reported two cases of spastic paraplegia in brother and sister, 10 and 7 years old respectively, born at term without complication, whose mother exhibited increased reflexes. He contends that clinical and anatomic considerations warrant the recognition of a disorder characterized clinically by spastic paraplegia and anatomically by primary system-sclerosis of the pyramidal fibres, either isolated or combined with degeneration of the columns of Goll. The ultimate cause still eludes detection. It may be toxic or infectious, perhaps syphilitic.

Erb (*Deutsche Zeitschrift für Nervenheilkunde*, Band VI, 1895, p. 137) reports two cases of spastic spinal paralysis in sisters, 12 and 6 years old respectively, in whose family history consanguinity was a prominent feature.

Jendrassik (*Deutsches Archiv für klinische Medicin*, Band LVIII, Hefte 2, 3, p. 137) has reported three families, in one of which a boy of 8 years presented symptoms of spastic paralysis, while the mother had an awkward gait from childhood, and a sister of 5 years had in-

creased reflexes; in another family a girl of 8 and a boy of 12 years exhibited symptoms of spastic paralysis; in the third family two sisters, 18 and 10 years old respectively, exhibited symptoms of spastic paralysis. In four of these cases there was advanced optic atrophy.

Ganghofner (*Zeitschrift für Heilkunde*, Band XVII, 1896, p. 303) has reported, among a series of cases of cerebral spastic paralysis, a brother and a sister presenting difficulty in walking, with weakness and trembling in the legs, scanning speech, ataxia of the upper extremities, increased knee-jerks and ankle-clonus, and in one also with strabismus.

Raymond and Souques (*Semaine Médicale*, 1896, p. 315) have reported the occurrence of progressive spastic paraplegia in two sisters, 19 and 15 years old respectively, both born at term, without difficulty. One brother and the paternal grandfather were chronic alcoholics.

Higier (*Deutsche Zeitschrift für Nervenheilkunde*, Band IX, 1896, Hefte 1, 2) reports four sisters, 24, 20, 18, and 17 years old respectively, who presented spastic manifestations, with tremor of the hands, dysphagia, bradylalia, strabismus, nystagmus, optic atrophy, defective intelligence, and muscular atrophy. The parents were cousins and the births had been normal. In all a diagnosis of cerebral spastic diplegia, with degeneration of the ganglion-cells of the anterior horns of the spinal cord, was made. Higier cites further two cases, in brothers, reported by Pribram (*Neurologisches Centralblatt*, 1895), and presenting symptoms of neural atrophy of peroneal type, in conjunction with those of cerebral diplegia. He also refers to a report by Melotti and Cantalemessa (*Revue neurologique*, 1896) of the occurrence of familial spastic paraplegia in two brothers and one sister, of whom a grandmother also was supposed to have suffered from the same disease. There had been no difficulty in birth. Finally, Higier cites the report by Koshewnikoff (*Meditzinskoje Obozrenije*,1895) of progressive spastic-paretic symptoms in two children in the same family attributed to cerebral diplegia.

Hochhaus (*Deutsche Zeitschrift für Nervenheilkunde*, Band IX, 1897, p. 291) has reported three cases of spastic spinal paralysis in a sister and two brothers 21, 13, and 8 years old respectively, all born at term without difficulty. He attributes the symptoms to disease of the lower segment of the pyramidal tracts, resulting from a congenital defect in development.

Of the cases here cited it must be evident that the lesions are not alike in all, as the clinical manifestations are not alike in all. In some there would appear to be cerebral lesions, either developmental or acquired, intrauterine, parturient, or postnatal. Even developmental defects must eventually be referred to some ultimate cause, as it is diffi-

cult to conceive of their spontaneous origin. Once established, however, they may be perpetuated by hereditary transmission. In cases of congenital spastic paralysis of cerebral origin, in which a history of difficult or protracted or complicated labor cannot be elicited, it is possible that the fetus may have been subjected to traumatism or have suffered from disease *in utero*. Ganghofner (*Zeitschrift für Heilkunde*, Band XVII, 1896, p. 303) attaches much importance to the influence of hereditary syphilis as an etiologic factor. Whilst the fetus is ordinarily well protected from physical injury, it may be that occasionally, from causes that escape scrutiny, this protection may be inadequate. Further, while dystocia may not be sufficient to delay labor notably, it may yet be sufficient to result in injury to the yielding and resilient calvarium of the fetus and its semifluid contents. The conditions favoring lesions of the cerebro-spinal axis of the fetus, either during the continuance of pregnancy or at parturition, once established, it is not surprising that occasionally more than one child in the same family should suffer from this cause.

In some of the cases it is probable that disseminated sclerosis or multiple lesions of other sort existed,—in some amyotrophic lateral sclerosis; while in a small number the symptoms of degeneration of the pyramidal tracts alone were present.

While existing evidence points to the possibility of primary lateral sclerosis, it is not so conclusive with regard to the isolated occurrence of this lesion, although the clinical testimony rather justifies its recognition. The explanation of the occasional familial distribution of the various disorders that have been under consideration in this communication must be sought in those indeterminate influences included in the term heredity, and it may be that these will be found to depend upon variations in cellular nutrition.

As an illustration of the familial distribution of cerebral spastic paralysis I shall detail a brief account of a family that came under my observation several years ago. Of nine children (six males and three females) of healthy parents three (two males and one female) presented classic symptoms of cerebral spastic paralysis. One (a male) had had a convulsion at the age of 14 months, but was in good health at the time of observation. Two (females) had died in infancy during dentition. Three (females) were quite well. There was no history of any difficulty in birth. One of the affected children had had an acute illness during childhood, following which speech was lost for several days and spastic symptoms appearing shortly afterwards. All three had suffered from measles at one time. No other etiologic influence could be determined.